


RESEARCH LETTER

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Angiotensin II infusion in COVID-19-associated vasodilatory shock: a case series

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Two thirds of ventilated COVID-19 patients require vasopressor support [1]. Recommended vasopressors include norepinephrine and vasopressin. Recently, based on a randomized trial [2], angiotensin II (ANGII) was FDA- and EMA-approved for catecholamine-resistant vasodilatory shock. ANGII use as primary vasopressor for vasodilatory shock has never been reported, let alone for COVID-19-associated vasodilatory shock. ANGII may be logical in this setting. It specifically assists patients recently exposed to angiotensin-converting enzyme inhibitors [2, 3] and increases the internalization and downregulation of angiotensin-converting enzyme 2 [4], the receptor for COVID-19. Its use may also inform the debate about the risks and benefits of angiotensin receptor blockers in COVID-19-infected patients [5]. In this pilot compassionate-use case series, we used ANGII either as primary or rescue vasopressor in ventilated patients with COVID-19-associated vasodilatory shock and assessed the course of key physiological variables during the first 48 h of treatment.

We studied a cohort of consecutive ventilated patients in COVID-19-dedicated ICUs at San Raffaele Scientific Institute, Milan, Italy. Patients had vasodilatory shock and COVID-19-related infection (positive viral RNA biospecimen and typical clinical and radiological features). The Ethics Committee approved compassionate use of the drug.

All cases received commercial ANGII (Giapreza®, La Jolla San Diego, CA) as continuous infusion started at 20 ng/kg/min and titrated to a MAP target > 65 mmHg. We collected key data before and during 48 h of angiotensin II infusion.

Over 6 days (March 12 to March 18, 2020) we treated 16 patients, 10 with ANGII as first-line agent, five as second-line agent (Table 1), and one patient with

unobtainable data. ANGII dose was relatively constant. MAP and urine output remained stable; lactate and creatinine increased and C-reactive protein decreased (Table 1). However, the SpO₂/FiO₂ ratio increased significantly with a decrease in FiO₂ and PEEP (Fig. 1). At latest follow-up (1 week), 14 patients were alive.

In ventilated patients with COVID-19-associated vasodilatory shock, we assessed the initial physiological changes associated with ANGII infusion as primary or rescue vasopressor. Overall, the administration of ANGII was associated with achievement and maintenance of target MAP, an increase on SpO₂/FiO₂ ratio, and a decrease in FiO₂. These oxygenation improvements were significant.

This represents the first experience with ANGII in COVID-19-associated vasodilatory shock and with ANGII as primary vasopressor in humans. The findings are consistent with those of a previous trial and subsequent subgroup [2] and ANG I/II ratio-related analyses [3]. They suggest the absence of early physiologically harm and improved oxygenation with ANG II.

The key limitations of this study are obvious. It is single-center, small, observational in nature; lacks a control population; and is open-label. However, in this pandemic setting, the ethics of ensuring compassionate drug use to all patients were considered a priority. Moreover, before considering controlled trials, evidence of some physiological safety was considered important. Finally, under the extraordinary pressures of the most dramatic health disaster in Italy's history in a century, this study was the best possible under the circumstances.

In conclusion, we provide the first observational cohort study of ANGII infusion in ventilated patients with COVID-19-associated vasodilatory shock. Our findings provide preliminary evidence to assist clinicians in their choice of vasopressors and justify and help design future controlled studies.

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Table 1 Baseline characteristics and physiological changes in treated patients

	Baseline (<i>n</i> = 15)	After 24 h (<i>n</i> = 15)	After 48 h (<i>n</i> = 15)
Age, years	64 (54–69)	–	–
Male gender	11 (73.3)	–	–
Angiotensin II as first-line agent	10 (66.7)	–	–
Angiotensin II dose, ng/kg/min	20.0 (5.0–20.0)	20.0 (8.4–20.8)	20.0 (8.1–20.8)
Support and drugs			
High dose catecholamine (> 0.25 µg/kg/min)	1 (6.7)	–	–
Receiving catecholamine > 12 h	2 (13.3)	–	–
Prone positioning	5 (41.7)	11 (78.6)	11 (78.6)
Use of tocilizumab	5 (35.7)	–	–
Norepinephrine dose, µg/kg/min	0.10 (0.10–0.20)	0.02 (0.00–0.09)	0.01 (0.00–0.14)
Hours using before	8.5 (1.8–15.8)	–	–
Vital signs at start			
Systolic arterial pressure, mmHg	110 (95–115)	110 (105–129)	120 (115–120)
Diastolic arterial pressure, mmHg	60 (52–64)	60 (56–64)	70 (59–70)
Mean arterial pressure, mmHg	71 (65–79)	77 (76–80)	85 (80–87)
Heart rate, bpm	82 (70–92)	72 (68–83)	71 (66–76)
Atrial fibrillation	1 (7.1)	–	–
Cumulative urine output, mL	237.5 (71.2–365.0)	620.0 (385.0–750.0)	727.0 (470.0–1050.0)
Oliguria	3 (30.0)	–	–
Ventilatory support			
FiO ₂	0.70 (0.61–0.70)	0.50 (0.40–0.60)	0.40 (0.36–0.54)
PEEP, cmH ₂ O	14 (12–15)	12 (10–12)	11 (10–14)
SpO ₂ , %	97 (94–99)	98 (96–98)	97 (91–98)
PaO ₂ /FiO ₂	121.4 (98.1–218.1)	195.2 (148.3–245.0)	200.0 (168.0–248.5)
SpO ₂ /FiO ₂	140.7 (132.5–150.6)	191.5 (118.4–258.0)	193.8 (142.2–235.9)
Laboratory tests at start			
Lactate, mmol/L	1.49 (1.36–1.56)	1.72 (1.58–2.00)	1.83 (1.53–2.15)
Creatinine, mg/dL	1.00 (0.85–1.68)	1.69 (1.16–2.38)	1.69 (1.06–2.43)
C-reactive protein, mg/dL	232.3 (165.4–269.2)	202.0 (148.4–231.1)	115.0 (95.0–190.4)
White blood cell count, × 1000 cells/mm ³	11.9 (7.7–13.2)	10.1 (6.2–12.4)	9.2 (7.2–14.2)
Lymphocyte count, × 1000 cells/mm ³	5.30 (3.05–16.222)	7.90 (3.70–12.85)	8.30 (5.20–13.50)

Data are median (quartile 25% to quartile 75%) or *N* (%)

PEEP positive end-expiratory pressure

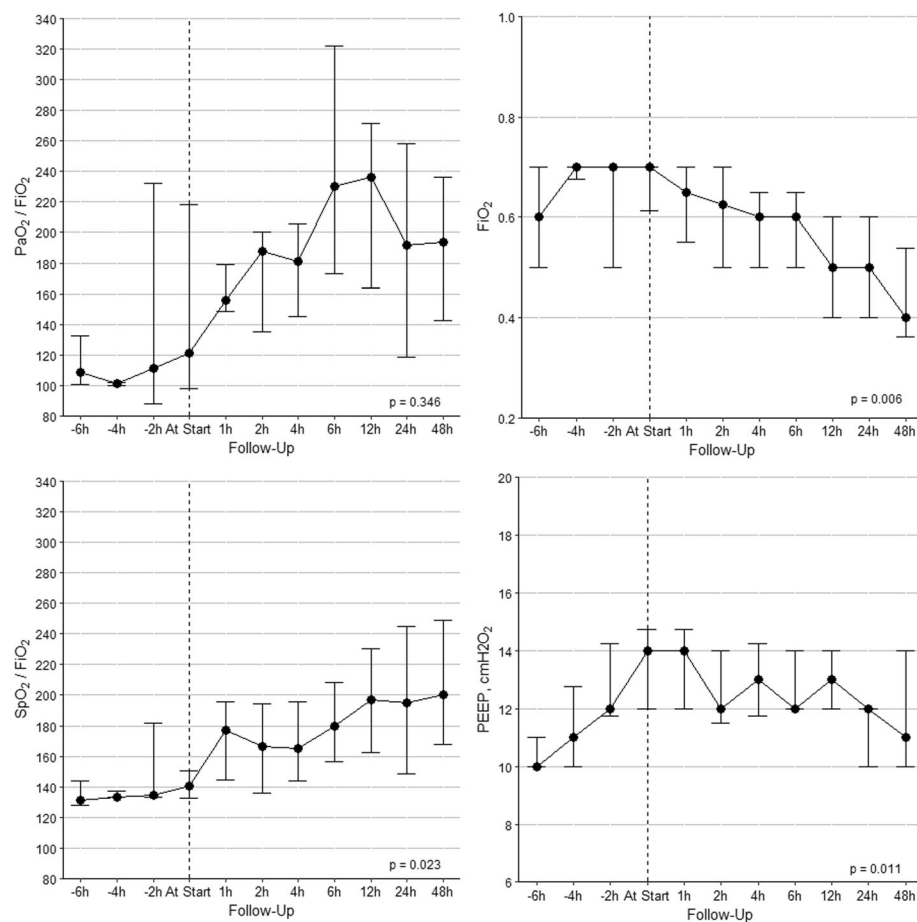


Fig. 1 Changes in oxygenation parameters in the first 48 h of angiotensin II infusion. Data are median and quartile 25% to quartile 75%. The changes in the parameters over time were assessed with a mixed-effect quantile model based on the asymmetric Laplace distribution ($\tau = 0.50$, a median regression), taking into account repeated measurements and considering the time of measurements (as a continuous variable) as fixed effect. The p value in the graphs represents the changes over this time. In all models, only values at and after the start of the infusion drug were taken into account, and the values before the start were used only for graphic purpose. All results were confirmed after bootstrapping with 10,000 replications. All analyses were conducted in R (R Foundation), version 3.6.3

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Authors' contributions

Concept: AZ, GL, and RB. Data collection: AZ, GL, LB, and FM. Data cleaning and statistical analysis: GL and ASN. Manuscript preparation: AZ, GL, ASN and RB. Administrative support: AZ, GL, and RB. The authors read and approved the final manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

Ethical Committee approved the compassionate use of the study drug for this study (which is approved by European Medical Association [EMA], but not yet commercialized).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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